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54 Title: Bone replacement material and its use

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Patent Claims

1. Bone replacement material, characterized by a biologically compatible and absorbable polymer that contains a filler that stimulates the absorption of the polymer in favor of newly formed bone tissue.

2. Bone replacement material according to Claim 1, characterized by the fact that the polymer has a high molecular weight so that the value of $\overline{M}p$ is 150,000 or more.

3. Bone replacement material according to one of the claims 1 or 2, characterized by the fact that the value of $\overline{M}p$ is above 200,000.

4. Bone replacement material according to one of the preceding claims, characterized by the fact that the polymer is a polymer with a low polydispersity index that is for example below 2.

5. Bone replacement material according to one of the preceding claims, characterized by the fact that the polymer is a homopolymer or copolymer of α-hydroxy acids.

6. Bone replacement material according to claim 5, characterized by the fact that the polymer is a homopolymer of glycolide, L-lactide, and/or D-lactide or a copolymer that is formed through the copolymerization of at least two of these monomers, including the copolymer of DL-lactide.

7. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler includes a material or is made out of a material that exerts a local stimulatory effect on bone growth.

8. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler contains salts based on phosphate anions or similar anions and/or salts based on calcium cations or analogous cations or mixtures of these salts.

9. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler consists of calcium phosphate and in particular tricalcium phosphate.

10. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler is present in an amount of 0.5 to 30%, based on the weight of the polymer.

11. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler is present in an amount of 0.5 to 5%, based on the weight of the polymer.

12. Bone replacement material according to one of the preceding claims, characterized by the fact that the filler has been added to the polymer in the form of a powder, the particles of which have a diameter of 1 to 20 μm.

13. Bone replacement material according to one of the preceding claims, characterized by the fact that it is in the form of a solid block, a granulate or a powder.

14. Use of the bone replacement material according to one of the preceding claims for the production of bone prostheses which are entirely or partly made of this material.

15. Use according to claim 14, characterized by the fact that the bone replacement material is used for the production of bone prosthetic parts such as solid parts, compound parts, parts made of inert material that are coated with the bone replacement material or parts made of an inert porous material that is impregnated with the bone replacement material.

16. Use according to claim 15, characterized by the fact that the bone replacement material is used for the production of solid parts that are produced by casting or by the machining of blocks.

17. Use according to claim 14, characterized by the fact that the bone material according to one of the claims 1 to 13 is used in the form of a granulate to replace losses of bone substance by filling with the material.

18. Bone prosthetic parts characterized by the fact that they consist entirely or partly of a material according to one of the claims 1 to 13.

19. Bone prosthetic parts according to claim 18, characterized by the fact that they include solid parts, compound parts, parts made of an inert material that is coated with the bone replacement material, or parts made of a porous material that is impregnated with the bone replacement material.

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INSTITUT NATIONAL DE LA SANTE
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<u>Bone replacement material and its use</u>

INSTITUT NATIONAL DE LA SANTE
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Case: DA 5506

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The present invention relates to a bone replacement material and its use for the production of bone prosthetic parts and the prosthetic parts thus obtained.

The expression used here, "prosthetic parts," includes both prosthetic parts in the traditional sense and also prosthetic parts for osteosynthesis.

In bone surgery (orthopedics and surgery of the upper jaw and face) at the present time, the anchoring of solid implants (joint prostheses and osteosynthetic prostheses) is achieved either by means of a cement (methyl methacrylate that is polymerized in situ), by means of metal screws in osteosynthesis or by nails (by means of a nail driven into the bone marrow). All these possibilities have various disadvantages, so that for several years research has aimed at the use of a porous material or one that can be absorbed in vivo, to accelerate the growing in again of the bone at the bone-implant interfaces.

The present invention makes it possible to solve this problem by the fact that prostheses or parts (plates and screws) suitable for osteosynthesis and coatings of prosthetic implants are used that consist of substances that simultaneously can be degraded biologically, favor bone growth and, if necessary depending on the purpose of application aimed at, possess appropriate mechanical properties (i.e. a modulus of elasticity that is similar to that of bone, or a sufficient breaking load or breaking strength to avoid a later rupture of the material).

The subject of the invention is thus a bone replacement material that is characterized by a biologically compatible or tissue-compatible and absorbable polymer that contains a filler that stimulates the absorption of the polymer in favor of newly formed bone tissue.

The invention bone replacement material thus makes it possible to combine in a single prosthetic part the properties of absorbability and activation of bone formation of the surrounding tissue.

The initial mechanical strength of the prosthetic part is determined by the selection of an appropriate polymer and the content of filler and can if necessary be improved by producing compound parts in which the invention bone replacement material is combined with reinforcement elements.

Polymers suitable for the production of the invention bone replacement material are preferably polymers of high molecular weight (with an $\bar{M}p$ value (weight-average molecular weight) of 150,000 or more and preferably of more than 200,000). According to the invention, it is especially preferred that polymers be used that contain a minimal amount of oligomers. Polymers are therefore used whose

polydispersity is low and is for example below 2.

Polymers that are suitable according to the invention can be homopolymers or copolymers.

Outstanding among the polymers that are suitable according to the invention are the polymers and copolymers of α-hydroxy acids and in particular the homopolymers and copolymers of glycolide and of L-, D-, and DL-lactides, because of their excellent biological compatibility and in particular their capacity to be degraded by the tissue. Based on their chemical structure and their properties, these polymers can serve as support material, can be degraded to non-toxic products that are excreted or made use of by the metabolism, and can over time be replaced by the living organism's own tissue that surrounds these polymers.

Among the polymers that are suitable according to the invention the homopolymers of glycolide, [redacted] stand out in particular. Particularly suitable copolymers are the products of the copolymerization of at least two of these monomers, in particular the L-lactide/glycolide copolymers, [redacted]glycolide copolymers, DL-lactide/glycolide copolymers and L-lactide/D-lactide/glycolide copolymers (including the DL-lactide copolymers).

The filler added for the formation of the invention bone replacement material is an inorganic and/or organic filler. The filler can consist of products that contain the following ions or some of them: lithium, borate, carbonate, fluoride, sodium, magnesium, silicate, potassium ions and their mixtures. In particular, salts based on phosphate ions or similar anions and/or salts based on calcium cations or other analogous cations or mixtures of these salts can be used. Preferred as filler are the calcium phosphates and in particular [redacted].

The filler can contain any material that exerts a locally stimulatory effect on bone growth, or can consist of such a material.

Very generally, the filler is present in an amount that is sufficient to fulfill the above-mentioned functions. In general, the filler is present in an [redacted], based on the weight of polymer. However, for a number of application purposes, and in particular when prosthetic parts are to be produced that have a relatively high mechanical strength, for example parts for the osteosynthesis of the long bones, materials are preferably used that contain the filler in an amount of 0.5 to 5%, based on the weight of the polymer.

Preferably, the filler is added in the form of a powder whose particles have a particle size of in particular 1 to 20μm.

The filler contained in the invention bone replacement material has the following effects:

The presence of the filler leads to the polymer mass having in it microscopic irregularities that facilitate the attack on certain sites of the material and thereby modify the absorbability of the material. A

physical effect is thus obtained. The particles of filler represent the preferred attack sites of the surface, with microscopic cavities being formed in which the newly formed bone develops preferentially.

This regeneration of bone is achieved at the expense of the formation of a capsular material (capsula fibrosa), which is one of the disadvantages that is observed with the conventional prosthetic parts.

Finally, in the invention bone replacement material, the filler is distributed in the entire mass and not only at the surface and thus represents a reserve of the base material for the bone regeneration that is released as absorption progresses.

On the basis of these effects, the following advantages result in particular:

The preferential attack of the invention bone replacement material at certain sites leads to a rough surface which leads to a larger interface and explains the internal bonding of the material to the bone that is observed in tissue sections and which also explains the fact that a firm anchoring of the prosthesis is achieved.

The absorption of the material is not accompanied by a weakening of the bone since because of the growing in of the regenerated bone material into the attack sites the strength and mechanical properties of the material are not impaired.

The polymers or copolymers used are compounds that are obtained by ring-opening polymerization using standard methods that are described in the literature. Particular attention must be devoted to the purity of the monomers and to the fact that the polymerization is carried out in such a way that masses with an elevated molecular weight (for example with an Mp value of $> 200{,}000$, a limiting viscosity number $[\eta]_{CHCl_3} > 1.6$ and a polydispersity index $I < 2$) are obtained that are free of oligomers and/or unpolymerized monomers. For example, the crude polymer can be purified by washing with a solvent for the monomers and/or oligomers.

The incorporation of the filler (which is also called the additive or adjuvant) can take place by means of well known methods of operation, i.e. by:

adding the filler in the form of a powder to a solution of the polymer and precipitating the material,

incorporating the filler into the molten polymer,

mixing the filler and the polymer in the powdered state and then grinding while warm,

introducing the filler into the polymerization medium at the beginning or in the course of the polymerization, or

using any other method that results in a homogeneous mixing of the additive or filler with the polymer mass.

As will be illustrated in more detail below, the invention bone replacement material is used for the production of prostheses or prosthetic parts by casting or mechanical processing or machining or also in the form of a granulate. The invention thus includes the bone replacement material both in the form of solid blocks and also in the form of granulates or powders (molding powders).

In molding powders, the particle size of the polymer particles is 1 to 100 μm and preferably 10 to 50 μm.

The subject of the invention is also the use of the defined bone replacement material for the production of bone prostheses that are produced completely or partly from this material.

Certain especially preferred executions of this application as well as the advantages that are achieved by means of the invention bone replacement material in certain forms of application are illustrated in more detail below:

a) Production of solid implant parts.

These parts are for example screws, plates, medullary nails for osteosynthesis and for fixing broken bones in the anatomically correct form. The later absorption of the material avoids a weakening or destruction of the synthesized bones and also avoids a second operation for the removal of the material. If the initial mechanical strength of the osteosynthetically formed union is insufficient for normal mobility to be achieved, healing can be favored by temporarily immobilizing the appropriate region of the body by means of a plaster cast or by splints.

These osteosynthetic prostheses or prosthetic parts have in particular the following advantages: on one hand, their absorption avoids a second surgical intervention, which generally follows a year after the fracture to remove the prosthesis or parts used in the osteosynthesis; on the other hand, the progressive degradation or progressive absorption of the material effectuates a gradual transfer of the stress from the osteosynthetic prosthesis or the osteosynthetic prosthetic part to the bone, whereby a fracture of the bone protected by the osteosynthetic plate is avoided which is generally observed in standard osteosynthetic methods of treatment. In fact, the bone is subject to a "sponge effect" when the dynamic stresses to which it is normally exposed are in fact taken up by the considerably stiffer osteosynthetic plate. Finally, a weakening or fragility of the bone during the period of collapse of the holes after the removal of the metal screws placed in the bone is avoided.

These prostheses or prosthetic parts can also be pieces with which losses of bone substance (after accidents or after the resection of bone tumors, etc.) are compensated. The definitive fitting of the prostheses and prosthetic parts used in the operation can for example be achieved by molding or modeling in the warm, if the materials are thermoplastic, which is the case with polylactic acid,

polyglycolic acid and their copolymers.

b) Coating of prostheses or prosthetic parts with an inert material.

For example, the femur end of a hip prosthesis can be coated with such a material, which makes possible a temporary fastening by nailing in the bone marrow cavity and favors the final fixation by stimulating bone growth on the contact surfaces of the implant, with this prosthesis coating replacing the cement interfaces that represent the main source of the observed loosening and the failure of these prostheses.

c) Impregnation of a porous inert material with the bone replacement material.

In prostheses, prosthetic parts or coatings made from a porous material (ceramic, metal, etc.) that is impregnated with the invention bone replacement material, the absorption of the impregnating material stimulates the regeneration of the bone into the open pores of the material that remains permanently, if the average measurements of the interconnected pores are about 0.1 to 1 mm.

d) The use of the invention bone replacement material in the form of a granulate with a particle size of a few tenths of millimeters up to a few millimeters.

These granulates can be used for the replacement of losses of bone substance. The regeneration of the bone takes place first of all in the intermediate space between the particles of the granulate and is then extended, depending on the absorption, on to the region of the granules. The improvement in the mechanical strength of the whole is accelerated by the stimulation of the growth of the bone.

The invention thus also relates to the use of the invention bone replacement material for the replacement of losses of bone substance by filling up these losses by means of the above-defined granulate.

The invention thus relates in particular to the use of the invention bone replacement material for the production of bone prostheses and bone prosthetic parts which is characterized by the fact that solid parts are produced from the bone replacement material or solid parts made of an inert material are provided with a coating of the bone replacement material, or that parts made of an inert porous material are impregnated with the invention bone replacement material.

The shaping into the items finally used (osteosynthetic plates, screws, etc.) can take place using any standard methods for the molding of thermoplastic polymer materials, such as injection molding, compression, machine-processing of blocks, etc., which in each case takes place depending on the target materials, which can also be compound materials or composite materials.

The invention thus also relates to bone prostheses or bone prosthetic parts that are produced completely or partly from the invention bone replacement material and in particular solid parts made from the

invention bone replacement material, parts that are coated with the invention bone replacement material or impregnated with it, as well as compound parts in which the mechanical properties of the invention bone replacement material are improved by biologically compatible support elements, for example polyethyleneterephthalate (Dacron) fibers.

It is moreover to be noted that the invention osteosynthetic plates make possible the electrical stimulation of bone formation as a supplementary treatment measure, without the electric signal being distorted.

The following examples serve for the further illustration of the invention.

Example 1

A polymerization tube is charged with 100 g L-lactide of high purity (recrystallized four times from methyl ethyl ketone), then a well-dried polymerization catalyst (250 mg zinc powder) is added. The mixture is degassed by repeated cooling and heating and treatment with nitrogen and evacuating, after which the polymerization tube is sealed under vacuum. The polymerization tube is put in a heated container and left there for 90 hours at 140°C. The polymer obtained is washed with dioxane over several hours. 90 g high-viscosity polymer is obtained that has all the properties of a high molecular weight poly-L-lactide (m.p. 174°C, the material is crystalline by x-ray diffraction, $[\eta]_{CHCl_3} = 1.74$, Young's modulus E 360 kg/mm^2).

Example 2

20 g of a copolymer containing 75% L-lactic acid units and 25% D-lactic acid units, in the form of a fine powder (with a particle size of 10 to 50 μm), is blended in the cold with 1 g powdered, dried calcium phosphate, until a homogeneous powder is obtained from the two components.

This powder is put into a compression mold and molded, at a temperature of 100 to 120°C using a pressure of 200 bar, to give a plate with the dimensions 90 x 15 x 4 mm., proceeding so that the formation of air inclusions is prevented.

Example 3

20 g glycolide is treated in a manner analogous to that in Example 1, but before the degassing of the mixture of monomer and catalyst 0.6 g calcium phosphate is added. The polymerization is effectuated under the conditions described in Example 1. It is however necessary to lengthen the reaction time to 8 to 10 days.

A macroscopically completely homogeneous material is obtained which can then be shaped in appropriate ways into prosthetic parts.

Example 4

20 g of the polymer obtained as in Example 1 is ground to a fine powder (with a particle diameter of 10 to 50 μm). This powder is blended with 0.2 g powdered tricalcium phosphate (with a particle diameter of 1 to 20 μm). A powder is obtained that can be used as a molding powder. This powder can be converted by heating into a syrupy mass that by extrusion and cutting up of the skein obtained affords a granulate with granules of dimensions 0.5 to 1 mm.

Example 5

On to the femur end of a hip prosthesis made of an anodically treated titanium/aluminum/vanadium alloy is applied a 0.5 to 1 mm thick layer of the polymer from Example 1, containing 1% calcium phosphate, the polymer being used in the molten state for this. The prosthetic part coated in this way is then pressed firmly into the medullary space of the femoral bone.

Analogously, the threads of screws used for the osteosynthesis are coated with the mixture of polymer and filler.

Example 6

The convex region of a porous ceramic joint socket (a joint prosthesis) made of sintered hydroxyapatite is impregnated in vacuum with a polymer that is identical to that prepared according to Example 3 but that contains as the filler not only calcium phosphate but also sodium fluoride. The impregnation mixture is applied in the molten state.

Parts of joint prostheses (for knee joints or shoulder joints) that are to be inserted into the joint sockets are analogously impregnated to anchor the prostheses.

Example 7

Plates and screws made of the polymer as in Example 1, containing 10% calcium phosphate, for osteosynthesis are implanted (without osteotomy) into sheep for 3 months. After the elapse of the stated period of time, the microscopic examination of histological sections shows that no significant presence of a capsular material (capsula fibrosa) is to be detected on the interfaces. There is thus a direct contact between the newly formed bone and the polymer. It is to be noted that the plates and screws used for the osteosynthesis were subjected to physiological stresses since the animals, living in freedom, moved about.